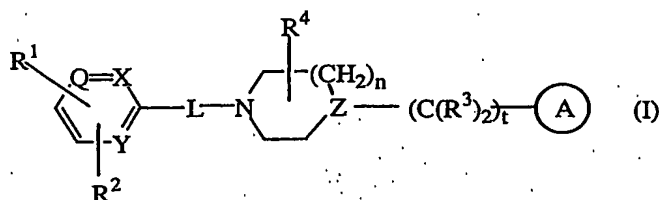


Claims

1. A compound of formula (I),



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

10 n is 0, 1, 2 or 3 and when n is 0 then a direct bond is intended;

t is 0, 1, 2, 3 or 4 and when t is 0 then a direct bond is intended;

each Q is nitrogen or —C= ;

15 each X is nitrogen or —C= ;

each Y is nitrogen or —C= ;

20 each Z is nitrogen or —CH= ;

R^1 is $\text{—C(O)NR}^7\text{R}^8$, —NHC(O)R^9 , $\text{—C(O)—C}_{1-6}\text{alkanediylSR}^9$, $\text{—NR}^{10}\text{C(O)N(OH)R}^9$, $\text{—NR}^{10}\text{C(O)C}_{1-6}\text{alkanediylSR}^9$, $\text{—NR}^{10}\text{C(O)C=N(OH)R}^9$ or another Zn-chelating-group

25 wherein R^7 and R^8 are each independently selected from hydrogen, hydroxy, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl or aminoaryl;

R^9 is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, aryl C_{1-6} alkyl, C_{1-6} alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R^{10} is independently selected from hydrogen or C_{1-6} alkyl;

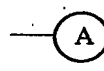
30 R^2 is hydrogen, halo, hydroxy, amino, nitro, C_{1-6} alkyl, C_{1-6} alkyloxy, trifluoromethyl, di(C_{1-6} alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;

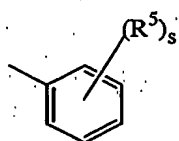
35 —L— is a direct bond or a bivalent radical selected from $\text{C}_{1-6}\text{alkanediyl}$, $\text{C}_{1-6}\text{alkanediylloxy}$, amino, carbonyl or aminocarbonyl;

BEST AVAILABLE COPY

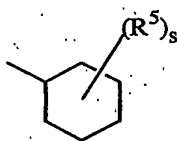
each R^3 independently represents a hydrogen atom and one hydrogen atom can be replaced by a substituent selected from aryl;

- 5 R^4 is hydrogen, hydroxy, amino, hydroxy C_{1-6} alkyl, C_{1-6} alkyl, C_{1-6} alkyloxy, aryl C_{1-6} alkyl, aminocarbonyl, hydroxycarbonyl, amino C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, hydroxycarbonyl C_{1-6} alkyl, hydroxyaminocarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylamino C_{1-6} alkyl or di(C_{1-6} alkyl)amino C_{1-6} alkyl;

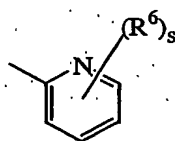
10  is a radical selected from



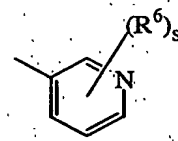
(a-1)



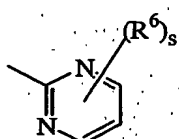
(a-2)



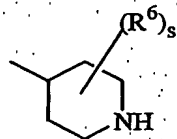
(a-3)



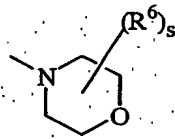
(a-4)



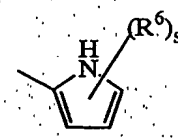
(a-5)



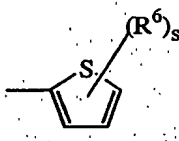
(a-6)



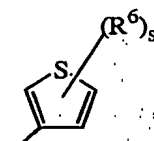
(a-7)



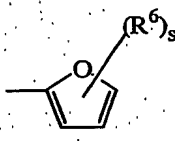
(a-8)



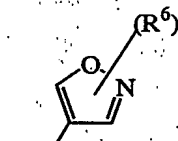
(a-9)



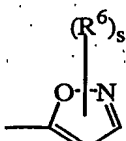
(a-10)



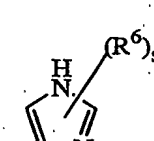
(a-11)



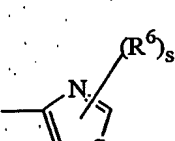
(a-12)



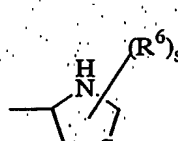
(a-13)



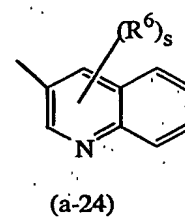
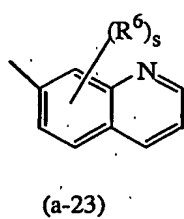
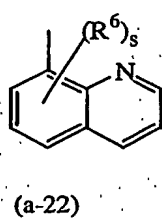
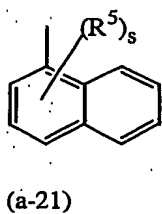
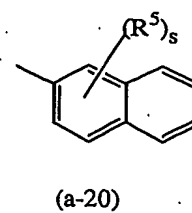
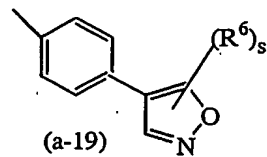
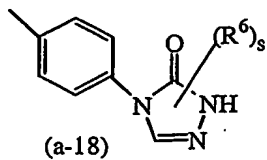
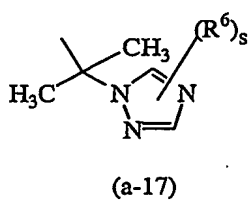
(a-14)



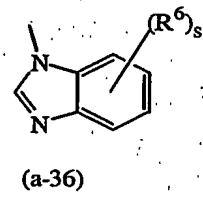
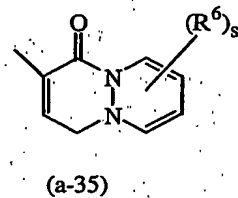
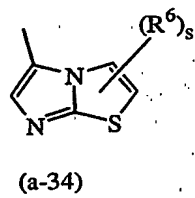
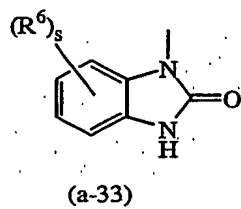
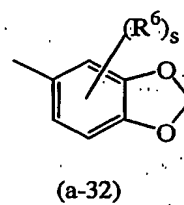
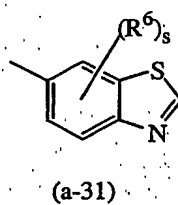
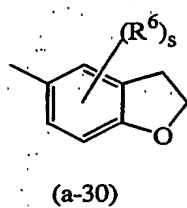
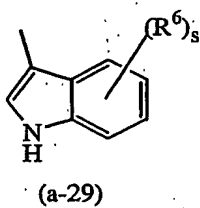
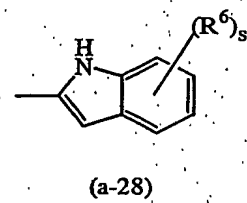
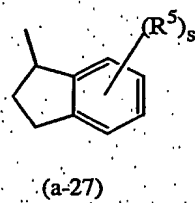
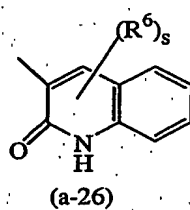
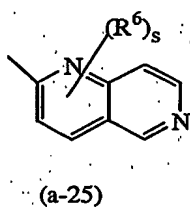
(a-15)



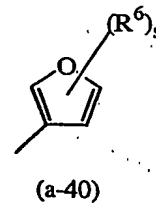
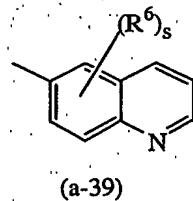
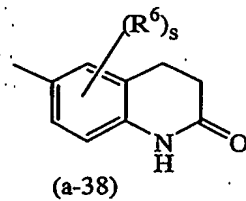
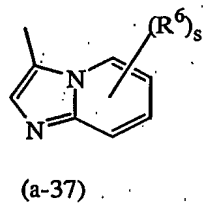
(a-16)

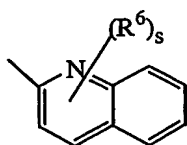


5

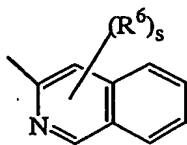


10

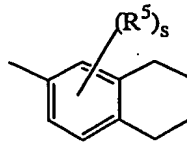




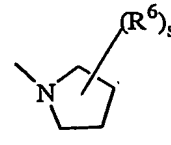
(a-41)



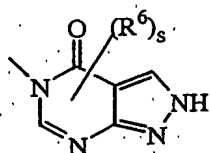
(a-42)



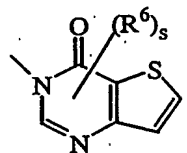
(a-43)



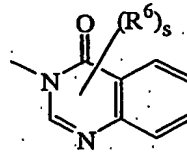
(a-44)



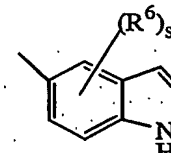
(a-45)



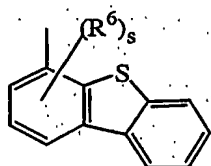
(a-46)



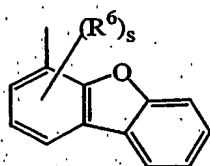
(a-47)



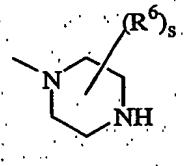
(a-48)



(a-49)



(a-50)



(a-51)

wherein each s is independently 0, 1, 2, 3, 4 or 5;

each R^5 and R^6 are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyl substituted with aryl and C₃₋₁₀cycloalkyl; C₁₋₆alkyloxy; C₁₋₆alkyloxyC₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; cyanoC₁₋₆alkyl; hydroxyC₁₋₆alkyl; hydroxyC₁₋₆alkyloxy; hydroxyC₁₋₆alkylamino; aminoC₁₋₆alkyloxy; di(C₁₋₆alkyl)aminocarbonyl; di(hydroxyC₁₋₆alkyl)amino; (aryl)(C₁₋₆alkyl)amino; di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy; di(C₁₋₆alkyl)aminoC₁₋₆alkylamino; di(C₁₋₆alkyl)aminoC₁₋₆alkylaminoC₁₋₆alkyl; arylsulfonyl; arylsulfonylamino; aryloxy; aryloxyC₁₋₆alkyl; arylC₂₋₆alkenediyl; di(C₁₋₆alkyl)amino; di(C₁₋₆alkyl)aminoC₁₋₆alkyl; di(C₁₋₆alkyl)amino(C₁₋₆alkyl)amino; di(C₁₋₆alkyl)amino(C₁₋₆alkyl)aminoC₁₋₆alkyl; di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)amino; di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl; aminosulfonylamino(C₁₋₆alkyl)amino; aminosulfonylamino(C₁₋₆alkyl)aminoC₁₋₆alkyl; di(C₁₋₆alkyl)aminosulfonylamino(C₁₋₆alkyl)amino; di(C₁₋₆alkyl)aminosulfonylamino(C₁₋₆alkyl)aminoC₁₋₆alkyl; cyano; thiophenyl; thiophenyl substituted with di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl; di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₆alkylpiperazinylC₁₋₆alkyl, hydroxyC₁₋₆alkylpiperazinylC₁₋₆alkyl,

hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinylC₁₋₆alkyl,
 di(C₁₋₆alkyl)aminosulfonylpiperazinylC₁₋₆alkyl,
 C₁₋₆alkyloxy piperidinyl, C₁₋₆alkyloxy piperidinylC₁₋₆alkyl, morpholinylC₁₋₆alkyl,
 hydroxyC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl, or di(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkyl;
 5 furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl; imidazolyl;
 oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl; C₁₋₆alkyltriazolyl; tetrazolyl;
 pyrrolidinyl; pyrrolyl; piperidinylC₁₋₆alkyloxy; morpholinyl; C₁₋₆alkylmorpholinyl;
 morpholinylC₁₋₆alkyloxy;
 morpholinylC₁₋₆alkyl; morpholinylC₁₋₆alkylamino;
 10 morpholinylC₁₋₆alkylaminoC₁₋₆alkyl; piperazinyl; C₁₋₆alkylpiperazinyl;
 C₁₋₆alkylpiperazinylC₁₋₆alkyloxy; piperazinylC₁₋₆alkyl;
 naphtalenylsulfonylpiperazinyl; naphtalenylsulfonylpiperidinyl; naphtalenylsulfonyl;
 C₁₋₆alkylpiperazinylC₁₋₆alkyl; C₁₋₆alkylpiperazinylC₁₋₆alkylamino;
 C₁₋₆alkylpiperazinylC₁₋₆alkylaminoC₁₋₆alkyl; C₁₋₆alkylpiperazinylsulfonyl;
 15 aminosulfonylpiperazinylC₁₋₆alkyloxy; aminosulfonylpiperazinyl;
 aminosulfonylpiperazinylC₁₋₆alkyl; di(C₁₋₆alkyl)aminosulfonylpiperazinyl;
 di(C₁₋₆alkyl)aminosulfonylpiperazinylC₁₋₆alkyl; hydroxyC₁₋₆alkylpiperazinyl;
 hydroxyC₁₋₆alkylpiperazinylC₁₋₆alkyl; C₁₋₆alkyloxy piperidinyl;
 C₁₋₆alkyloxy piperidinylC₁₋₆alkyl; piperidinylaminoC₁₋₆alkylamino;
 20 piperidinylaminoC₁₋₆alkylaminoC₁₋₆alkyl;
 (C₁₋₆alkylpiperidinyl)(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkylamino;
 (C₁₋₆alkylpiperidinyl)(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkylaminoC₁₋₆alkyl;
 hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinyl;
 hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinylC₁₋₆alkyl;
 25 (hydroxyC₁₋₆alkyl)(C₁₋₆alkyl)amino; (hydroxyC₁₋₆alkyl)(C₁₋₆alkyl)aminoC₁₋₆alkyl;
 hydroxyC₁₋₆alkylaminoC₁₋₆alkyl; di(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkyl;
 pyrrolidinylC₁₋₆alkyl; pyrrolidinylC₁₋₆alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl
 substituted with two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl;
 pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl;
 30 tetrahydropyrimidinylpiperazinyl; tetrahydropyrimidinylpiperazinylC₁₋₆alkyl;
 quinolinyl; indole; phenyl; phenyl substituted with one, two or three substituents
 independently selected from halo, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy,
 hydroxyC₁₋₄alkyl, trifluoromethyl, trifluoromethyloxy, hydroxyC₁₋₄alkyloxy,
 C₁₋₄alkylsulfonyl, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkyloxycarbonyl,
 35 aminoC₁₋₄alkyloxy, di(C₁₋₄alkyl)aminoC₁₋₄alkyloxy, di(C₁₋₄alkyl)amino,
 di(C₁₋₄alkyl)aminocarbonyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)aminoC₁₋₄alkylaminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)amino(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)amino(C₁₋₄alkyl)aminoC₁₋₄alkyl,

di(C₁₋₄alkyl)aminoC₁₋₄alkyl(C₁₋₄alkyl)amino,
 di(C₁₋₄alkyl)aminoC₁₋₄alkyl(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 aminosulfonylamino(C₁₋₄alkyl)amino,
 aminosulfonylamino(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 5 di(C₁₋₄alkyl)aminosulfonylamino(C₁₋₄alkyl)amino,
 di(C₁₋₄alkyl)aminosulfonylamino(C₁₋₄alkyl)aminoC₁₋₆alkyl, cyano,
 piperidinylC₁₋₄alkyloxy, pyrrolidinylC₁₋₄alkyloxy, aminosulfonylpiperazinyl,
 aminosulfonylpiperazinylC₁₋₄alkyl, di(C₁₋₄alkyl)aminosulfonylpiperazinyl,
 di(C₁₋₄alkyl)aminosulfonylpiperazinylC₁₋₄alkyl, hydroxyC₁₋₄alkylpiperazinyl,
 10 hydroxyC₁₋₄alkylpiperazinylC₁₋₄alkyl, C₁₋₄alkyloxy piperidinyl,
 C₁₋₄alkyloxy piperidinylC₁₋₄alkyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkylpiperazinyl,
 hydroxyC₁₋₄alkyloxyC₁₋₄alkylpiperazinylC₁₋₄alkyl,
 (hydroxyC₁₋₄alkyl)(C₁₋₄alkyl)amino, (hydroxyC₁₋₄alkyl)(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 di(hydroxyC₁₋₄alkyl)amino, di(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkyl, furanyl, furanyl
 15 substituted with -CH=CH-CH=CH-, pyrrolidinylC₁₋₄alkyl, pyrrolidinylC₁₋₄alkyloxy,
 morpholinyl, morpholinylC₁₋₄alkyloxy, morpholinylC₁₋₄alkyl,
 morpholinylC₁₋₄alkylamino, morpholinylC₁₋₄alkylaminoC₁₋₄alkyl, piperazinyl,
 C₁₋₄alkylpiperazinyl, C₁₋₄alkylpiperazinylC₁₋₄alkyloxy, piperazinylC₁₋₄alkyl,
 C₁₋₄alkylpiperazinylC₁₋₄alkyl, C₁₋₄alkylpiperazinylC₁₋₄alkylamino,
 20 C₁₋₄alkylpiperazinylC₁₋₄alkylaminoC₁₋₆alkyl, tetrahydropyrimidinylpiperazinyl,
 tetrahydropyrimidinylpiperazinylC₁₋₄alkyl, piperidinylaminoC₁₋₄alkylamino,
 piperidinylaminoC₁₋₄alkylaminoC₁₋₄alkyl,
 (C₁₋₄alkylpiperidinyl)(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkylamino,
 (C₁₋₄alkylpiperidinyl)(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkylaminoC₁₋₄alkyl,
 25 pyridinylC₁₋₄alkyloxy,
 hydroxyC₁₋₄alkylamino, hydroxyC₁₋₄alkylaminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)aminoC₁₋₄alkylamino, aminothiadiazolyl,
 aminosulfonylpiperazinylC₁₋₄alkyloxy, or thiophenylC₁₋₄alkylamino;
 each R⁵ and R⁶ can be placed on the nitrogen in replacement of the hydrogen;

30 aryl in the above is phenyl, or phenyl substituted with one or more substituents each
 independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, cyano or
 hydroxycarbonyl.

- 35 2. A compound as claimed in claim 1 wherein n is 1 or 2; t is 0, 1, 2 or 4; each Q is
 $\text{—C}\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$; R¹ is -C(O)NH(OH); R² is hydrogen or nitro; -L- is a direct bond or a
 bivalent radical selected from C₁₋₆alkanediyl; R⁴ is hydrogen; $\text{—}\bigcirc\text{A}$ is a radical

selected from (a-1), (a-2), (a-3), (a-5), (a-6), (a-11), (a-18), (a-20), (a-21), (a-32), (a-33), (a-47) or (a-51); each s is independently 0, 1, 2, or 4; each R⁵ and R⁶ are independently selected from hydrogen; halo;

trihaloC₁₋₆alkyl; C₁₋₆alkyl; C₁₋₆alkyl substituted with aryl and C₃₋₁₀cycloalkyl;

5 C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; benzofuranyl; naphthalenylsulfonyl; pyridinyl substituted with aryloxy; phenyl; or phenyl substituted with one substituent independently selected from hydroxyC₁₋₄alkyl or morpholinylC₁₋₄alkyl.

3. A compound as claimed in claim 1 wherein t is 1, 2, 3, or 4;

10 R¹ is -C(O)NR⁷R⁸, -C(O)-C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)N(OH)R⁹, -NR¹⁰C(O)C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)C=N(OH)R⁹ or another Zn-chelating-group wherein R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, hydroxyC₁₋₆alkyl or aminoC₁₋₆alkyl;

R² is hydrogen, halo, hydroxy, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl or
15 di(C₁₋₆alkyl)amino;

-L- is a direct bond or a bivalent radical selected from C₁₋₆alkanediyl, C₁₋₆alkanediylloxy, amino or carbonyl;

R⁴ is hydrogen, hydroxy, amino, hydroxyC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy, arylC₁₋₆alkyl, aminocarbonyl, aminoC₁₋₆alkyl, C₁₋₆alkylaminoC₁₋₆alkyl or
20 di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

—(A)— is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44), (a-45), (a-46), (a-47), (a-48) and (a-51);

each s is independently 0, 1, 2, 3 or 4;

R⁵ is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy;

C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl;

C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano;

30 thiophenyl; furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl;

imidazolyl; oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl;

C₁₋₆alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl;

C₁₋₆alkylmorpholinyl; piperazinyl;

C₁₋₆alkylpiperazinyl; hydroxyC₁₋₆alkylpiperazinyl;

35 C₁₋₆alkyloxypiperidinyl; pyrazolyl; pyrazolyl substituted with one or two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl; pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl; quinolinyl; indole;

phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl;

R⁶ is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy;

C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl;

5 C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano; pyridinyl;

phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl.

4. A compound as claimed in claim 1 and 2 wherein n is 1; t is 0 or 1; each Q is

10 $\text{—C}\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$; each X is nitrogen; each Y is nitrogen; R¹ is

—C(O)NH(OH); R² is hydrogen; —L— is a direct bond; each R³ independently

represents a hydrogen atom; R⁴ is hydrogen; $\text{—}\bigcirc\text{(A)}$ is a radical selected from

(a-6), (a-11), (a-20), (a-47) or (a-51); each s is independently 0, 1, or 4; and each R⁵

and R⁶ are independently selected from hydrogen; C₁₋₆alkyl; C₁₋₆alkyloxy;

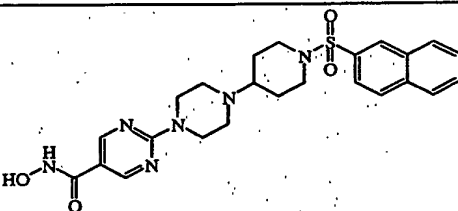
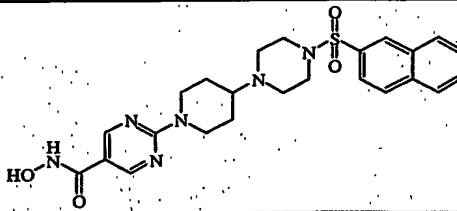
15 naphthalenylsulfonyl; or phenyl substituted with hydroxyC₁₋₄alkyl or

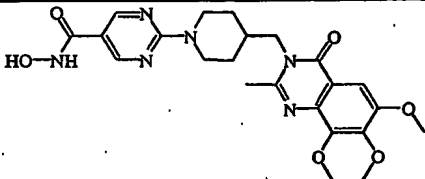
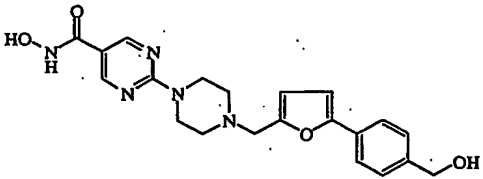
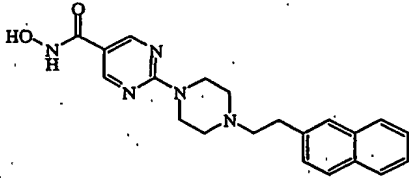
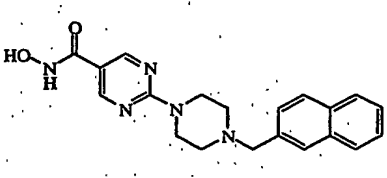
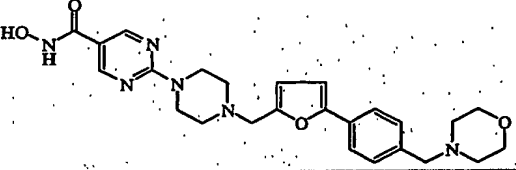
morpholinylC₁₋₄alkyl.

5. A compound according to claim 1, 2 and 4 selected from compounds No. 3, No.

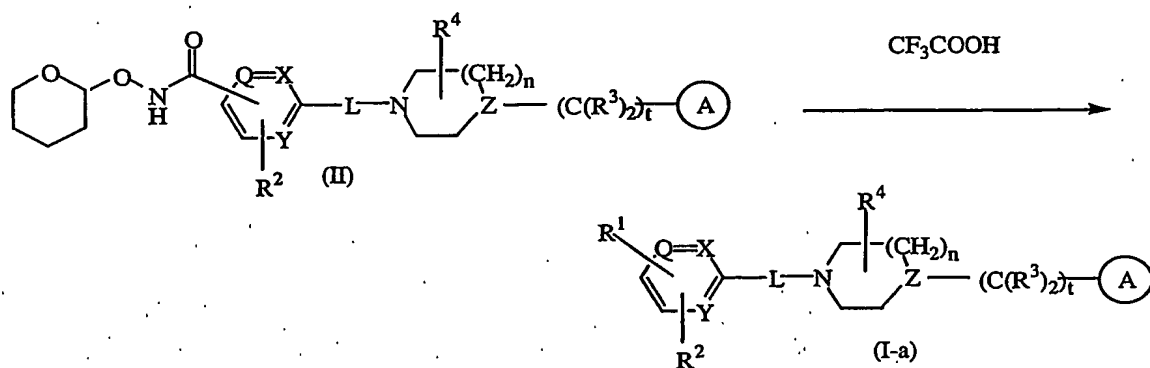
4, No. 8, No. 5, No. 7, No. 6 and No. 9.

20

	
0.91 C ₂ HF ₃ O ₂ ; Co. No. 3	0.86 C ₂ HF ₃ O ₂ ; Co. No. 4

	
C ₂ HF ₃ O ₂ (1:1); Co. No.8	0.83 C ₂ HF ₃ O ₂ ; Co. No.5
	
0.79 C ₂ HF ₃ O ₂ ; Co. No.7	0.83 C ₂ HF ₃ O ₂ ; Co. No.6
	
0.47 H ₂ O .1.99 C ₂ HF ₃ O ₂ ; Co. No.9	

6. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 5.
7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 5 are intimately mixed.
8. A compound as claimed in any of claims 1 to 5 for use as a medicine.
9. Use of a compound as claimed in any of claims 1 to 5 for the manufacture of a medicament for the treatment of proliferative diseases.
10. A process for preparing a compound as claimed in claim 1, characterized by reacting an intermediate of formula (II) with an appropriate acid, such as for example, trifluoro acetic acid, yielding a hydroxamic acid of formula (I-a), wherein R¹ is -C(O)NH(OH)



11. A method of detecting or identifying a HDAC in a biological sample comprising detecting or measuring the formation of a complex between a labelled compound as defined in claim (I) and a HDAC.
12. A combination of an anti-cancer agents and a HDAC inhibitor as claimed in any of claims 1 to 5.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.